REMARKS

Applicant amends the claims to remove multiple dependencies, to provide proper antecedent basis, and to address other matters of form. The foregoing amendments introduce no new matter and are not related to issues of patentability.

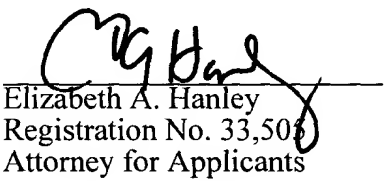
Entry of the foregoing Preliminary Amendment is respectfully in order and requested.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims by the current amendments. Appendix A is captioned "Version With Markings To Show Changes Made." Also attached hereto as Appendix B is a complete set of the claims that will be pending upon entry of the amendments presented herein.

If there are any questions regarding the amendments to the application, we invite the Examiner to call Applicant's representative at the telephone number below.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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Date: **27 August 2001**

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please amend claims 6, 9, 11, 13, 14, 15, 18, 19, 25, 28, 30, and 35 as follows.

6. (Amended) A compound which is substantially complementary to a protein according to ~~any one of~~ claim~~s~~ 1~~-5~~.

9. (Amended) An isolated complex, which is comprised of a protein according to claim~~s~~ 1~~-5~~ and a complementary compound according to ~~any one of~~ claim~~s~~ 6~~-8~~, wherein the three-dimensional structure of LTA_4 hydrolase is essentially as disclosed in Table 9 by the parameters defining atom 1- atom 4876, or a functionally equivalent part, derivative or conformational analogue of such a complex.

11. (Amended) Use of the parameters of a protein according to ~~any one of~~ claim~~s~~ 1~~-5~~, a compound according to ~~any one of~~ claim~~s~~ 6~~-8 or a complex according to claim 9 or 10~~ in drug design, such as in molecular modeling, direct structure-based design and/or combinatorial chemistry.

13. (Amended) Use according to claim 11 ~~or 12~~, wherein said drug is for the treatment and/or prevention of disorders involving acute and chronic inflammatory and/or allergic symptoms, said disorder being selected from the group consisting of arthritis, inflammatory bowel disease (IBD), psoriasis, chronic obstructive pulmonary disease (COPD), and acquired immune deficiency syndrome (AIDS).

14. (Amended) Use according to claim 11 ~~or 12~~, wherein said drug is for the treatment and/or prevention of proliferative disorders, such as neoplasias and/or cancer.

15. (Amended) Use according to claim 11 ~~or 12~~, wherein said drug is for the treatment and/or prevention of disorders caused by the lethal factor of *Bacillus anthracis,* e.g. anthrax.

18. (Amended) A method according to claim 16 ~~or 17~~, wherein an enzymatic inhibitor complementary to the amino acids defined in ~~any one of~~ claim~~s~~ 3~~, 4 or 5~~ is screened for.

19. (Amended) An analogue obtainable by the method ~~according to any one~~ of claim~~s~~ 16~~-18~~.

25. (Amended) A compound obtainable by the method according to ~~any one of~~ claim~~s~~ 21~~-24~~.

28. (Amended) A process for the purification of a protein according to ~~any one of~~ claim~~s~~ 1~~-3~~ or obtained according to claim 26~~ or 27~~, which purification includes hydroxyapatite-based chromatography and a subsequent anion exchange chromatography.

30. (Amended) A protein obtained by the method according to ~~any one of~~ claim~~s~~ ~~27-29~~ 26.

35. (Amended) A protein according to any one of claims 6~~-8~~, 25, 30 or 31 for use as a medicament.

APPENDIX B

1. An isolated protein comprising at least a subsequence of the amino acid sequence of LTA_4 hydrolase, which exhibits a three-dimensional form essentially as disclosed in Table 9 by the parameters defining atom 1 to atom 4876, said subsequence being capable of participating in the control of the enzymatic pathway, such as the leukotriene cascade, or a functionally equivalent part, derivative or conformational analogue thereof.

2. A protein according to claim 1, which comprises an enzymatically active site defined in the following table:

	Left Wall	Right Wall
1		Lys608, Asp606, Lys605, Lys354, Thr355
2	Phe356, Phe362	Gln544, Asp573, Lys572, Arg568
3	Val376	Lys565, Arg540, Leu507
4	Ser380, Ser352, Glu348	Pro569
5	Tyr378, Glu348	Arg563, Glu533, Phe536, Arg537, Tyr267
6	Tyr383, Phe314, Glu318, Glu384, Arg326	
7	Gly268, Gly269, Met270	His295, Asn341, Phe340
8	Ser288, His497	Glu325, Asn291

3. A protein according to claim 2, which is an enzyme having a metallohydrolase activity capable of participating in the regulation of enzyme activities in biochemical pathways, wherein said enzymes have structures similar to the ones defined in claim 2.

4. A protein according to claim 1, which comprises an enzymatically active site defined by the following amino acids: Gln136; Ala137; Tyr267; Gly268; Gly269; Met270; Glu271; Val292; His295; Glu296; His299; Glu318; Tyr378; Tyr383; Arg563; Lys565.

5. A protein according to claim 1, which comprises an enzymatically active site defined by the following amino acids: Gln136; Ala137; Tyr267; Gly268; Gly269; Met270; Glu271; Va1292; His295; Glu296; His299; Trp315; Glu318; Val322; Phe362; Va1367; Leu369; Pro374; Asp375; Ile372; Ala377; Pro382; Tyr378; Tyr383; Arg563; Lys565.

6. A compound which is substantially complementary to a protein according to claim 1.

7. A compound according to claim 6, which is substantially complementary to an enzymatically active site of said protein and which is capable of specifically inhibiting said enzymatic activity.

8. A compound according to claim 7, which is an inhibitor of a metallohydrolase enzyme.

9. An isolated complex, which is comprised of a protein according to claim 1 and a complementary compound according to claim 6, wherein the three-dimensional structure of LTA_4 hydrolase is essentially as disclosed in Table 9 by the parameters defining atom 1- atom 4876, or a functionally equivalent part, derivative or conformational analogue of such a complex.

10. A complex according to claim 9, wherein the protein complexed with LTA_4 hydrolase is selected from the group which consists of bestatin, thiolamine or hydroxamic acid or a functionally equivalent part, derivative or conformational analogue of such a complex.

11. Use of the parameters of a protein according to claim 1, a compound according to claim 6 in drug design, such as in molecular modeling, direct structure-based design and/or combinatorial chemistry.

12. Use according to claim 11, wherein said parameters are selected from the parameters disclosed in Table 9 defining atom 1- atom 4876.

13. Use according to claim 11, wherein said drug is for the treatment and/or prevention of disorders involving acute and chronic inflammatory and/or allergic symptoms, said disorder being selected from the group consisting of arthritis, inflammatory bowel disease (IBD), psoriasis, chronic obstructive pulmonary disease (COPD), and acquired immune deficiency syndrome (AIDS).

14. Use according to claim 11, wherein said drug is for the treatment and/or prevention of proliferative disorders, such as neoplasias and/or cancer.

15. Use according to claim 11, wherein said drug is for the treatment and/or prevention of disorders caused by the lethal factor of *Bacillus anthracis,* e.g. anthrax.

16. A method for screening LTA_4 hydrolase hydrolase analogues that mimic at least a part of 5 the three-dimensional structure of the LTA_4 hydrolase molecule as defined by the parameters shown in Table 9 for atom 1 to atom 4876, which comprises the steps of
(a) producing a multiplicity of analogue structures of LTA_4 hydrolase and
(b) selecting an analogue structure, wherein the three-dimensional configuration and spatial arrangement of one or more enzymatically active sites and/or binding sites of said LTA_4 hydrolase remain substantially preserved.

17. A method according to claim 16, wherein an analogue exhibiting an enzymatic activity, such as an epoxide hydrolase and/or aminopeptidase activity, is selected.

18. A method according to claim 16, wherein an enzymatic inhibitor complementary to the amino acids defined in claim 3 is screened for.

19. An analogue obtainable by the method of claim 16.

20. An analogue according to claim 19, which exhibits an increased catalytic activity when compared to the naturally occurring form of LTA_4 hydrolase, such as defined in Table 9 by parameters of atom 1 to atom 4876.

21. A method for screening LTA_4 hydrolase binding compounds complementary to a region of LTA_4 hydrolase, preferably an enzymatically active site thereof, which comprises the steps of

(a) producing a multiplicity of possible complementary structures and

(b) selecting a structure, wherein the three-dimensional configuration and spatial arrangement of regions involved in binding to LTA_4 hydrolase remain substantially preserved, which selection is based on the three-dimensional structure of LTA_4 hydrolase, and/or LTA_4 hydrolase complexed to an inhibitor thereof, in a form adopted thereof in nature, such as defined in Table 9.

22. A method according to claim 21, wherein a general metallohydrolase inhibitor is selected, which is capable of inhibiting an enzyme belonging to the M1 family.

23. A method according to claim 21, wherein an inhibitor of the epoxide hydrolase activity and/or aminopeptidase activity of LTA_4 hydrolase or of LTA_4 syntheses is selected.

24. A method according to claim 21, wherein a compound capable of antagonizing LTB_4 receptor binding of a cell is selected.

25. A compound obtainable by the method according to claim 21.

26. A method of engineering a protein, which method comprises the steps of

- identification of a suitable set of mutations based on the structure of LTA_4 hydrolase;
- generation of a library of genes which contains the suitable sequence variations;

- selection of clones encoding the LTA_4 hydrolase analogues with a desired activity function;

wherein said desired activity is the capability of efficiently producing an organic compound of interest.

27. A method according to claim 26, wherein the specified property is the suicidal mode of action of LTA_4 hydrolase.

28. A process for the purification of a protein according to claim 1 or obtained according to claim 26, which purification includes hydroxyapatite-based chromatography and a subsequent anion exchange chromatography.

29. A process for the crystallization of an LTA_4 hydrolase, an analogue or a derivative thereof, wherein said crystallisation is performed with the addition of an ytterbium salt as an additive, such as an ytterbium chloride.

30. A protein obtained by the method according to claim 26.

31. A protein according to claim 30, which is present in an essentially pure form.

32. An isolated nucleic acid encoding a protein according to claim 30 or 31.

33. A nucleic acid capable of specifically hybridising to a nucleic acid according to claim 32.

34. Use of a protein, which is a genetically modified LTA_4 hydrolase, according to claim 30 or 31 in the preparation of LTB_4 or other metabolites in the leukotriene cascade.

35. A protein according to any one of claims 6, 25, 30 or 31 for use as a medicament.